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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/651,661	08/29/2003	David H. Dolphin	273012012010	9324

25225 7590 07/27/2006

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EXAMINER	
PERREIRA, MELISSA JEAN	

ART UNIT	PAPER NUMBER
1618	

DATE MAILED: 07/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/651,661	DOLPHIN ET AL.	
	Examiner	Art Unit	
	Melissa Perreira	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 August 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 August 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/8/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 11-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of chelating a metal to an agent of the instant claims, does not reasonably provide enablement for a method of inhibiting a metalloenzyme. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Attention is directed to In re Wands, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing Ex parte Forman, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,
2) the amount of direction or guidance provided,
3) the presence or absence of working examples,
4) the nature of the invention,
5) the state of the prior art,
6) the relative skill of those in the art,
7) the predictability of the art, and
8) the breadth of the claims.

The instant specification fails to provide guidance that would allow the skilled artisan to practice the instant invention without resorting to undue experimentation, as discussed in the subsections set forth hereinbelow.

Nature of the invention, State in the art , Relative skill of those in the art and Predictability of the art

Metalloenzymes are naturally occurring mammalian enzymes that employ metal cations directly in a functional capacity. There are numerous superfamilies of metalloenzymes as well as numerous metalloenzymes included in those families, such as matrix metalloproteins and tumor nectorsis factor converting enzyme. The multidisciplinary study of metalloenzymes includes chemisty, microbiology, biochemistry and molecular biology and the limited understanding of the structure and function of metalloenzymes is due to their occurrence in various biological systems with the discovery of new proteins containing metals. The predictability of the inhibition of a metalloenzyme would be limited in that it is possible for an enzyme to chelate one or more metal ions in the active state or that multiple inhibitors may be used for the inhibition of the same metalloenzyme, for example the inhibition of zinc-metalloenzymes are known to be inhibited by phosphate ions (US 5,989,803). Metal-detoxification methods used are reversible bimetallic crosslinking strategies of covalently binding reagents to DNA-binding proteins, which bind metal ions as an integral part of their function, as well as high affinity coordination complexes utilizing disulfide bond or vicinal thiols which form cleavable bonds to proteins (US 5,534,542). Metallothioneins is a biological compound known to bind to cadmium, copper and zinc and has been studied due to its putative role in cadmium detoxification (US 6,932,980B1).

The quantity of experimentation, Amount of direction or guidance provided and The presence or absence of working examples

The lack of adequate guidance from the specification or prior art with regard to the actual treatment fails to rebut the presumption of unpredictability present in this art. Applicants fail to provide the guidance and information required to ascertain which particular metalloenzyme the claimed agent will be effective in inhibiting, how the metalloenzyme will be inhibited, why it is necessary to inhibit the metalloenzymes or which metal the agent will chelate without resorting to undue experimentation. Applicant's limited disclosure of the method of inhibition of a metalloenzyme is not sufficient to justify claiming all broadly.

Breadth of the claims

The claims are very broad and inclusive of "inhibiting a metalloenzyme" which includes all metalloenzymes. They do not include which metal would be chelated by the agent of the instant claims so would include all metals, such as zinc which is known to be an abundant metal in the body and is required for many biological processes.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 1,4,5,7,9,11,14,15,17 and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Bruckner et al. (Abs Pacifichem 95).

5. Bruckner et al. (Abs Pacifichem 95) teaches of a di(pyrrolyl)thioketone, a diamagnetic Ni(II)-N,S-chelate and a Cd (II) complex and a 2-pyrrolyl-aryl thioketone (p2 and 4).

6. Claim 1,4 and 7 are rejected under 35 U.S.C. 102(b) as being anticipated by Bruckner et al. (*J. Porphyrins Phthalocyanines* **1998**, *2*, 455-465).

7. Bruckner et al. (*J. Porphyrins Phthalocyanines* **1998**, *2*, 455-465) teaches of the synthesis and use of di-2-pyrrolyl-thione (p 457, paragraph 2). The di-2-pyrrolyl-thione is a precursor for the synthesis of 5,15-diphenylporphyrin (DPP).

8. Claims 1,4,5 and 7 are rejected under 35 U.S.C. 102(b) as being anticipated by Clezy et al. (*Aust. J. Chem.* **1969**, *22*, 239).

9. Clezy et al. (*Aust. J. Chem.* **1969**, *22*, 239) discloses thiocarbonyl compounds such as di(N,N-dimethylamino)phenyl substituted thiocarbonyls, N,N'-dimethyl-2,2'-dipyrrylthione IVe (p 243, fig; paragraph 2).

10. The compounds above can be used as a diagnostic or therapeutic imaging agent precursor as products of identical chemical composition and can not have mutually exclusive properties. A chemical composition and its properties are inseparable. Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable and does not render the old composition patentably new to the discoverer. In re Best, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977)

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

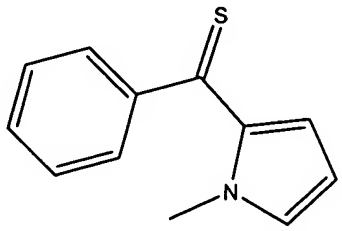
12. Claims 1,4,5,7,9,11,14,15,17 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bruckner et al. (Abs Pacifichem 95) in view of the combined disclosures of Jurrison et al. (*Chem. Rev.* **1993**, *93, 1137-1158*) and Lumbroso et al (*J. Mol. Struct.* **1984**, *112*, 85-99).

13. Bruckner et al. (Abs Pacifichem 95) teaches of a di(pyrrolyl)thioketone, a diamagnetic Ni(II)-N,S-chelate and a Cd (II) complex and a 2-pyrrolyl-aryl thioketone (p2 and 4) but does not teach of a radiopharmaceutical with ^{99m}Tc suitable for diagnostic imaging.

14. Jurrison et al. (*Chem. Rev.* **1993**, *93, 1137-1158*) discloses the use of ^{99m}Tc for radiopharmaceuticals and is used in 90% of diagnostic scans performed in nuclear medicine (p 1140, paragraph 1).

15. Lumbroso et al (*J. Mol. Struct.* **1984**, *112*, 85-99) discloses the corresponding thioketone of 2-benzoyl-N-methylpyrrole (abstract).

2-benzoyl-N-methylpyrrole corresponding thioketone



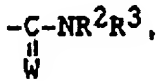
At the time of the invention it would have been obvious to one ordinarily skilled in the art to chelate a Technetium-99m in place of nickel, such as Bruckner et al. (Abs Pacifichem 95) to obtain a radiopharmaceutical. Technetium-99m has favorable physical properties, widespread availability and low cost, as well as a half-life is long enough to do the necessary chemistry but it is short enough as to minimize the radiation dose to the patient. The use and preparation of variously substituted thioketones is necessitated by the need for more stable and organ specific compounds for diagnostic imaging. The substitution of pyrrole for a phenyl ring or other alkyl, aryl, heterocycle or others listed in the instant claims would be obvious to try to generated the least toxic and most effective diagnostic imaging agent. Also, dipyrrylketones have few properties typical of carbonyl compounds due to the mesomeric contributions from the resonance structures and the same considerations should apply to the structures of dipyrrylthiones.

16. Claims 1-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bruckner et al. (Abs Pacifichem 95) and Jurrison et al. (*Chem. Rev.* **1993**, *93, 1137-1158*) in view of the combined disclosures of Williams et al. (EP 0530907A1), Middleton (US 2,940,977) and Brown et al. (US 5,310,938).

17. Bruckner et al. (Abs Pacifichem 95) teaches of a di(pyrrolyl)thioketone, a diamagnetic Ni(II)-N,S-chelate and a Cd (II) complex and a 2-pyrrolyl-aryl thioketone (p2 and 4) but does not teach of a carboxymethyl substituted phenyl substituent or a SO_3H substitutent synthesized via dioxane sulfotrioxide.

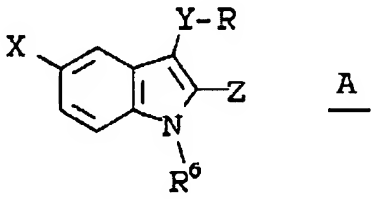
18. Jurrison et al. (*Chem. Rev.* **1993**, *93, 1137-1158*) discloses the use of ^{99m}Tc for radiopharmaceuticals and is used in 90% of diagnostic scans performed in nuclear medicine (p 1140, paragraph 1).

19. Williams et al. (EP 0530907A1) discloses a compound A (below) where Y is SO_2, R is H, R_6 is H, Z is



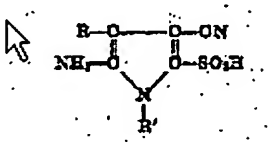
and W is S (p3, lines 13-15),.

Novel compounds of formula A:

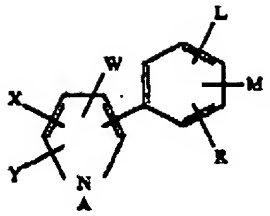


A

20. Middleton (US 2,940,977) discloses a sulfonic acid adjacently substituted on a pyrrole ring where R' is H (below; column 1) and the sodium salt (column 3, lines 4-6).



21. Brown et al. (US 5,310,938) discloses substituted arylpyrrole compounds for the treatment and prevention of infection (abstract; below) where L can be F, Cl, Br or R_2CO and R_2 is C_{1-3} alkyl, such as methyl (column 1, line 63; column 2, line 11).



At the time of the invention it would have been obvious to one ordinarily skilled in the art to substitute a SO_3H for a SO_2H group of Williams et al. (EP 0530907A1) to alter the reactivity of the compound to make it a better chelator and a more effective diagnostic imaging agent by allowing for easier passage into a cell due to a more hyrdrophyllic substitutent.. Altering the substitution pattern by placing the SO_3H on a carbon position adjacent to the N of the pyrrole as is disclosed in Middleton (US 2,940,977) or substituting the phenyl with a carboxymethyl would be some of the various substitutions and patterns one would try to generate the least toxic and most effective diagnostic imaging agent.

Double Patenting

22. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140

F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

23. Claims 1-9 and 11-19 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 15 of U.S. Patent No. US 6,613,304. Although the conflicting claims are not identical, they are not patentably distinct from each other because the diagnostic imaging or therapeutic agent of US 6,613,304 requires and discloses the diagnostic imaging or therapeutic agent precursor of the instant claims as well as the composition comprising the agent and the chelation of a metal, such as Tc, Re and others listed in the instant claims to the diagnostic imaging or therapeutic agent precursor.

Conclusion

No claims are allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Melissa Perreira whose telephone number is 571-272-1354. The examiner can normally be reached on 9am-5pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MP
July 10, 2006

MICHAEL G. HARTLEY
SUPERVISORY PATENT EXAMINER